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Signed

Dated

M. Russell
29th Nov 91.

21 JUN 1991

21 JUN 1991

Your reference

T1092GB

25JUN 91 00301194 PAT 1 77 UC 15.00

91134155

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The Patent Office

Request for grant of a Patent

Form 1/77

Patents Act 1977

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① Title of invention

1 Please give the title of the invention Therapeutic Agents

② Applicant's details

First or only applicant

2a If you are applying as a corporate body please give:

Corporate name Merck Sharp & Dohme Limited

Country (and State of incorporation, if appropriate) United Kingdom

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c In all cases, please give the following details:

Address Hertford Road
Hoddesdon
Hertfordshire

UK postcode (if applicable) EN11 9BU

Country United Kingdom
ADP number (if known) 00597799001 ✓

2d, 2e and 2f: If there are further applicants please provide details on a separate sheet of paper.

Second applicant (if any)

- 2d If you are applying as a corporate body please give:

Corporate name

Country (and State
of incorporation, if
appropriate)

- 2e If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

- 2f **In all cases**, please give the following details:

Address

UK postcode
(if applicable)

Country

ADP number
(if known)

③ An address for service in the United Kingdom must be supplied

Please mark correct box

Yes No **go to 3b**

please give details below

Agent's name Dr. J. Thompson

Agent's address Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow, Essex
CM20 2QR

Postcode

Agent's ADP
number 4392742002 ✓

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

- 3b If you have not appointed an agent please give a name and address in the United Kingdom to which all correspondence will be sent:

Name

Address

Postcode

Daytime telephone
number (if available)

ADP number
(if known)

④ Reference number

4 Agent's or applicant's reference number (if applicable) T1092GB

⑤ Claiming an earlier application date

- 5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes No

please give details below

number of earlier application or patent number

filing date

(day month year)

and the Section of the Patents Act 1977 under which you are claiming:

15(4) (Divisional) 8(3) 12(6) 37(4)

⑥ If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

⑥ Declaration of priority

- 6 If you are declaring priority from previous application(s), please give:

Country of filing	Priority application number (if known)	Filing date (day, month, year)

- 7** The answer must be 'No' if:
- any applicant is not an inventor
 - there is an inventor who is not an applicant, or
 - any applicant is a corporate body.

8 Please supply duplicates of claim(s), abstract, description and drawing(s).

7 Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

Please mark correct box

Yes No **A Statement of Inventorship on Patents
Form 7/77 will need to be filed (see Rule 15).**

8 Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77

Claim(s)	-	Description	67
Abstract	-	Drawing(s)	-

8b Which of the following documents also accompanies the application?

Priority documents (please state how many)

Translation(s) of Priority documents (please state how many)

Patents Form 7/77 – Statement of Inventorship and Right to Grant
(please state how many)

Patents Form 9/77 – Preliminary Examination/Search

Patents Form 10/77 – Request for Substantive Examination

Please mark correct box(es)

9 You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.

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Dr. J. Thompson
Chartered Patent Agent

Date 21.06.91
(day month year)

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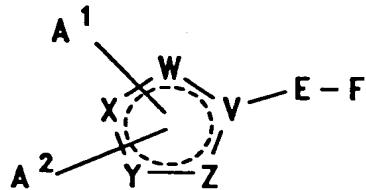
THERAPEUTIC AGENTS

5 The present invention relates to a class of indole-substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT₁-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

10 5-HT₁-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, The Lancet, 1988, Vol. 1, 1309-11). The compounds of the present 15 invention, being selective 5-HT₁-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

20 EP-A-0313397 describes a class of tryptamine derivatives substituted by a five-membered heteroaliphatic ring, which are stated to be specific to a particular type of "5-HT₁-like" receptor and thus to be effective therapeutic agents for the treatment of 25 clinical conditions, particularly migraine, requiring this activity. However, EP-A-0313397 neither discloses nor suggests the imidazole, triazole and tetrazole derivatives provided by the present invention.

30 The present invention provides a compound of formula I, or a salt or prodrug thereof:



(1)

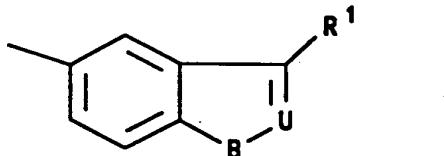
wherein the broken circle represents two non-adjacent
10 double bonds in any position in the five-membered ring;
two, three or four of V, W, X, Y and Z
represent nitrogen and the remainder represent carbon
provided that, when two of V, W, X, Y and Z represent
15 nitrogen and the remainder represent carbon, then the
said nitrogen atoms are in non-adjacent positions within
the five-membered ring;

A¹ represents hydrogen, hydrocarbon, halogen,
cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY,
-NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTNR^XRY;

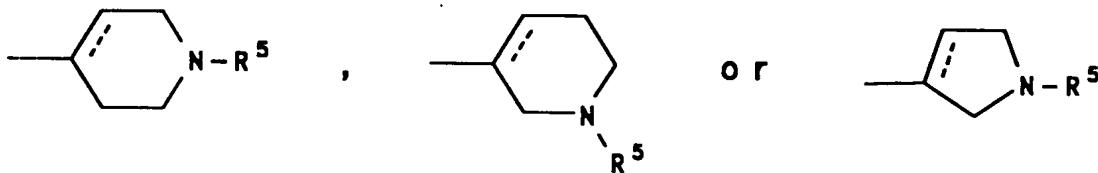
20 A² represents a non-bonded electron pair when
four of V, W, X, Y and Z represent nitrogen and the other
represents carbon; or, when two or three of V, W, X, Y
and Z represent nitrogen and the remainder represent
carbon, A² represents hydrogen, hydrocarbon, halogen,
25 cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY,
-NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTNR^XRY;

E represents a bond or a straight or branched
alkylene chain containing from 1 to 4 carbon atoms;

F represents a group of formula



10 U represents nitrogen or C-R²;
 B represents oxygen, sulphur or N-R³;
 R¹ represents -CH₂.CHR⁴.NR⁶R⁷ or a group of
 formula



in which the broken line represents an optional chemical bond;

25 R², R³, R⁴, R⁵, R⁶ and R⁷ independently
 represent hydrogen or C₁₋₆ alkyl;

 R^X and R^Y independently represent hydrogen or
 hydrocarbon, or R^X and R^Y together represent a C₂₋₆
 alkylene group;

 R^Z represents hydrogen or hydrocarbon;

30 T represents oxygen, sulphur or a group of
 formula =N.G; and

 G represents hydrocarbon or an electron-
 withdrawing group.

The present invention also provides compounds
of formula I above wherein three or four of V, W, X, Y

and Z represent nitrogen and the remainder represent carbon;

A² represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A² represents hydrogen, hydrocarbon, halogen, cyano, trifluoromethyl, -OR^X, -SR^X, -NR^XRY, -NR^XCORY, -NR^XCO₂RY, -NR^XSO₂RY, or -NR^ZCTNR^XRY; and

A¹, E, F, R^X, R^Y, R^Z and T are as defined above.

For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups, including heterocyclic groups, containing up to 18 carbon atoms,

suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁-6 alkyl, C₂-6 alkenyl, C₂-6 alkynyl, C₃-7 cycloalkyl, C₃-7 cycloalkyl(C₁-6)alkyl, aryl, aryl(C₁-6)alkyl, C₃-7 heterocycloalkyl, C₃-7 heterocycloalkyl(C₁-6)alkyl, 5 heteroaryl and heteroaryl(C₁-6)alkyl.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl 10 groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 15 6 carbon atoms. Typical examples include vinyl and allyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and 20 propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

A particular aryl group is phenyl.

Particular aryl(C₁-6)alkyl groups include 25 benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, 30 quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C₁-6)alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon group may in turn be optionally substituted by one or more groups selected from C₁-6 alkyl, adamantyl, phenyl, halogen, C₁-6 haloalkyl, C₁-6 aminoalkyl, trifluoromethyl, hydroxy, C₁-6 alkoxy, aryloxy, keto, C₁-3 alkylenedioxy, nitro, cyano, carboxy, C₂-6 alkoxycarbonyl, C₂-6 alkoxycarbonyl(C₁-6)alkyl, C₂-6 alkylcarbonyloxy, arylcarbonyloxy, C₂-6 alkylcarbonyl, 10 arylcarbonyl, C₁-6 alkylthio, C₁-6 alkylsulphanyl, C₁-6 alkylsulphonyl, arylsulphonyl, -NR^VR^W, -NR^VCOR^W, -NR^VCO₂R^W, -NR^VSO₂R^W, -CH₂NR^VSO₂R^W, -NHCONR^VR^W, -CONR^VR^W, -SO₂NR^VR^W and -CH₂SO₂NR^VR^W, in which R^V and R^W independently represent hydrogen, C₁-5 alkyl, aryl or 15 aryl(C₁-6)alkyl, or R^V and R^W together represent a C₂-6 alkylene group.

When R^X and R^Y, or R^V and R^W, together represent a C₂-6 alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or 20 hexamethylene group, preferably butylene or penta-methylene.

When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, -COR^X, -CO₂R^X or -SO₂R^X, in which R^X is as defined above.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially 25 fluorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for 30

example, in "Design of Prodrugs", ed. H. Bundgaard,
Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

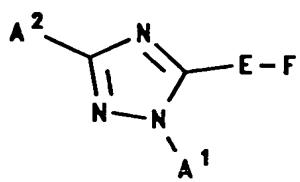
It will be appreciated that the imidazole, triazole and tetrazole rings of formula I can exist in a variety of canonical forms. These may suitably be represented by formulae IA to IT as follows:

15

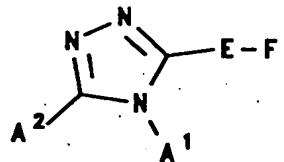
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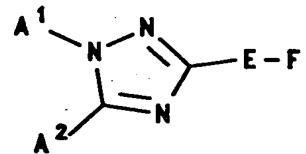
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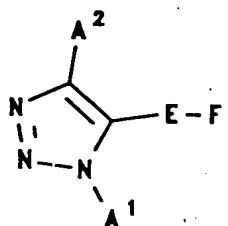
(IA)



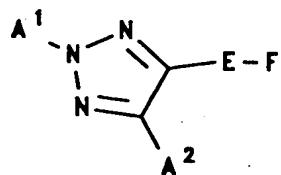
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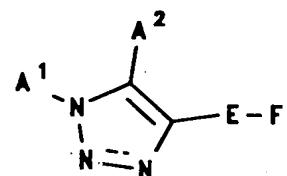
(IC)



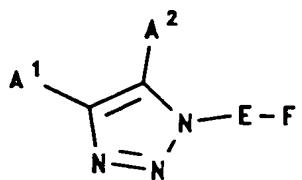
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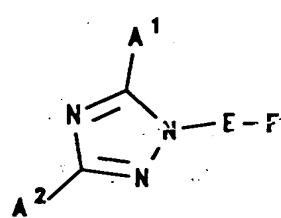
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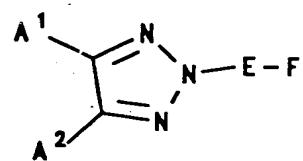
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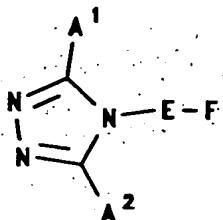
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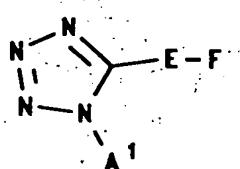
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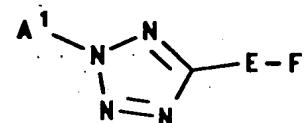
(IJ)



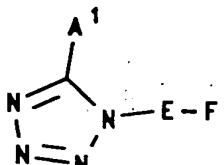
(I K)



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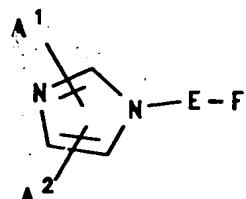
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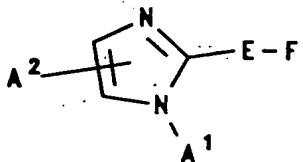
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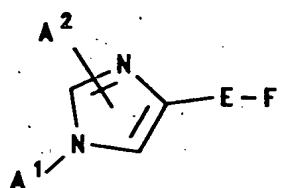
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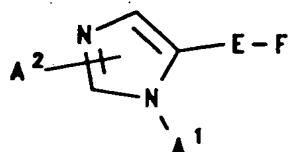
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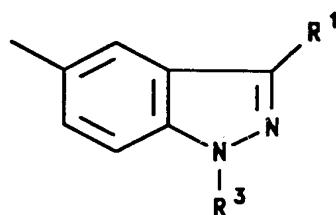
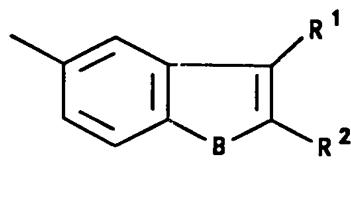
(I T)

wherein A¹, A², E and F are as defined above. Preferred imidazole, triazole and tetrazole rings of formula I include the rings represented by formulae IA, IC, IG, IH, IL, IM, IN, IP and IQ above, especially IH.

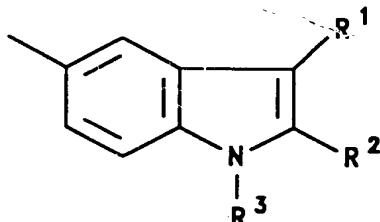
The alkylene chain E may be, for example, methylene, ethylene, 1-methylethylene, propylene or

2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the five-membered heteroaromatic ring.

- 5 The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:



wherein B, R¹, R² and R³ are as defined above. Preferably, the group F represents an indole moiety of structure FC:



wherein R¹, R² and R³ are as defined above, in particular wherein R² and R³ are both hydrogen.

- 30 It will be appreciated that when four of V, W, X, Y and Z represent nitrogen and the other represents carbon, i.e. when the ring of formula I is a tetrazole ring, then the group A² will be a non-bonded electron pair. Otherwise, A¹ and A² will independently represent

hydrogen, hydrocarbon, halogen, cyano, trifluoromethyl, $-OR^X$, $-SR^X$, $-NR^XRY$, $-NR^XCORY$, $-NR^XCO_2RY$, $-NR^XSO_2RY$ or $-NR^ZCTNR^XRY$.

Suitable values for the groups A^1 and/or A^2 include C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted; and hydrogen, halogen, cyano, trifluoromethyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio or $-NR^XRY$, in which R^X and R^Y are as defined above. Examples of optional substituents on the groups A^1 and/or A^2 suitably include trifluoromethyl, C₁₋₆ alkoxy, C₂₋₆ alkoxycarbonyl, C₂₋₆ alkylcarbonyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, amino, mono- or di(C₁₋₆)alkylamino, C₂₋₆ alkylcarbonylamino, arylcarbonylamino, C₂₋₆ alkoxycarbonylamino, C₁₋₆ alkylsulphonylamino, arylsulphonylamino, C₁₋₆ alkylsulphonylaminomethyl, aminocarbonylamino, mono- or di(C₁₋₆)alkylaminocarbonyl-amino, mono- or diarylaminocarbonylamino, pyrrolidylcarbonylamino, aminocarbonyl, mono- or di(C₁₋₆)alkylaminocarbonyl, C₁₋₆ alkylaminosulphonyl, aminosulphonylmethyl, and mono- or di(C₁₋₆)-alkylaminosulphonylmethyl.

Particular values of A^1 and/or A^2 include hydrogen, methyl, methoxymethyl, aminomethyl, dimethylaminomethyl, acetylaminomethyl, benzoylaminomethyl, t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetylamoethyl, benzoylamoethyl, methoxycarbonylamoethyl, ethoxycarbonylamoethyl, t-butoxycarbonylamoethyl, methylsulphonylamoethyl, aminocarbonylamoethyl, methylaminocarbonylamoethyl, t-butylaminocarbonyl-aminoethyl, phenylaminocarbonylamoethyl,

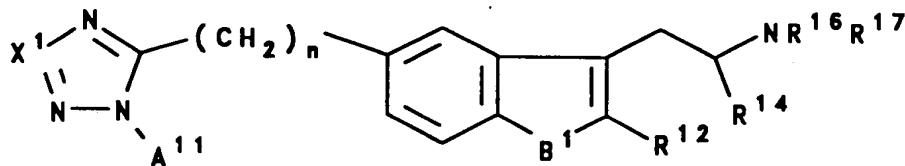
pyrrolidylcarbonylaminoethyl, cyclopropyl, phenyl,
methylsulphonylaminophenyl, aminocarbonylphenyl,
methylaminocarbonylphenyl, methylsulphonylaminomethyl-
phenyl, aminosulphonylmethylphenyl, methylaminosulphonyl-
methylphenyl, dimethylaminosulphonylmethylphenyl, benzyl,
trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl,
methylsulphonylaminobenzyl, aminocarbonylaminobenzyl,
aminocarbonylbenzyl, methylaminocarbonylbenzyl,
methylsulphonylbenzyl, methylaminosulphonylbenzyl,
5 pyridylmethyl, methoxypyridylmethyl, amino, methylamino,
benzylamino, dimethylamino, t-butoxycarbonylamino-
ethylamino and methylsulphonylaminethylamino.

Preferred values of A¹ and/or A² include
hydrogen, methyl and benzyl.

15 Representative values of R¹ include aminoethyl,
N-methylaminoethyl, N,N-dimethylaminoethyl and 1-methyl-
4-piperidyl. Preferably, R¹ represents aminoethyl or
N,N-dimethylaminoethyl.

20 Preferred values for the groups R² to R⁷ are
hydrogen and methyl.

A particular sub-class of compounds according
to the invention is represented by the compounds of
formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

x¹ represents nitrogen or A¹²-C;
n is zero, 1, 2 or 3;

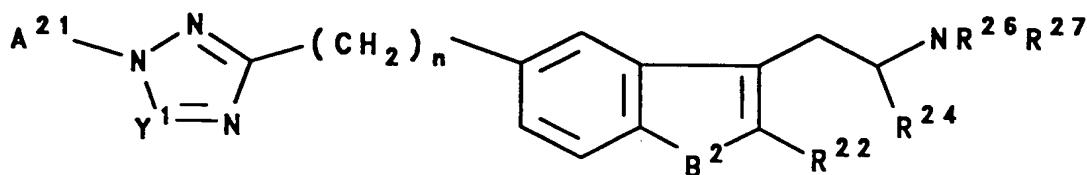
- B¹ represents oxygen, sulphur or N-R¹³;
A¹¹ and A¹² independently represent C₁₋₆ alkyl,
C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl,
aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl or
heteroaryl(C₁₋₆)alkyl, any of which groups may be
optionally substituted; or hydrogen, halogen, cyano,
trifluoromethyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio or -NR^XR^Y;
R¹², R¹³, R¹⁴, R¹⁶ and R¹⁷ independently
represent hydrogen or C₁₋₆ alkyl; and
R^X and R^Y independently represent hydrogen or
hydrocarbon, or R^X and R^Y together represent a C₂₋₆
alkylene group.

Examples of optional substituents on the groups
A¹¹ and A¹² suitably include trifluoromethyl, C₁₋₆
alkoxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkyl carbonyl, C₁₋₆
alkylsulphonyl, arylsulphonyl, amino, mono- or
di(C₁₋₆)alkylamino, C₂₋₆ alkyl carbonylamino,
arylcarbonylamino, C₂₋₆ alkoxy carbonylamino, C₁₋₆
alkylsulphonylamino, arylsulphonylamino, C₁₋₆
alkylsulphonylaminomethyl, aminocarbonylamino, mono- or
di(C₁₋₆)alkylaminocarbonylamino, mono- or diaryl amino-
carbonylamino, pyrrolidyl carbonylamino, aminocarbonyl,
mono- or di(C₁₋₆)alkylaminocarbonyl, C₁₋₆ alkylamino-
sulphonyl, aminosulphonylmethyl, and mono- or
di(C₁₋₆)alkylaminosulphonylmethyl.

Particular values of A¹¹ and A¹² with respect
to formula IIA include hydrogen, methyl, benzyl and
amino. When X¹ represents A¹²-C, the group A¹¹ is
preferably hydrogen or methyl.

Preferably, R¹², R¹³ and R¹⁴ each represents
hydrogen. Preferred values of R¹⁶ and R¹⁷ with respect
to formula IIA include hydrogen and methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:



(IIB)

wherein

Y¹ represents nitrogen or A²²-C;

15 n is zero, 1, 2 or 3;

B² represents oxygen, sulphur or N-R²³;

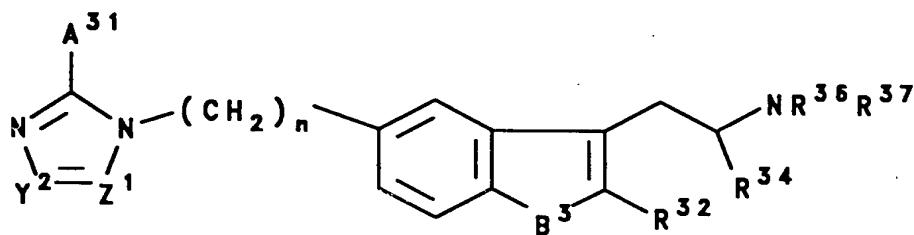
A²¹ and A²² independently represent C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio or -NR^XRY; R²², R²³, R²⁴, R²⁶ and R²⁷ independently represent hydrogen or C₁₋₆ alkyl; and

25 R^X and R^Y independently represent hydrogen or hydrocarbon, or R^X and R^Y together represent a C₂₋₆ alkylene group.

Examples of optional substituents on the groups A²¹ and A²² correspond to those indicated for the groups A¹¹ and A¹² with respect to formula IIA above. Particular values of A²¹ and A²² with respect to formula IIB include hydrogen, methyl and benzyl.

Preferably, R²², R²³ and R²⁴ each represents hydrogen. Preferred values of R²⁶ and R²⁷ with respect to formula IIB include hydrogen and methyl.

5 A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

Y² represents nitrogen or A³²-C;

Z¹ represents nitrogen or CH;

n is zero, 1, 2 or 3;

20 B³ represents oxygen, sulphur or N-R³³;

A³¹ and A³² independently represent C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, aryl, aryl(C₁₋₆)alkyl, C₃₋₇ heterocycloalkyl, heteroaryl or heteroaryl(C₁₋₆)alkyl, any of which groups may be 25 optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio or -NR^XRY, R³², R³³, R³⁴, R³⁶ and R³⁷ independently represent hydrogen or C₁₋₆ alkyl; and

30 R^X and R^Y independently represent hydrogen or hydrocarbon, or R^X and R^Y together represent a C₂₋₆ alkylene group.

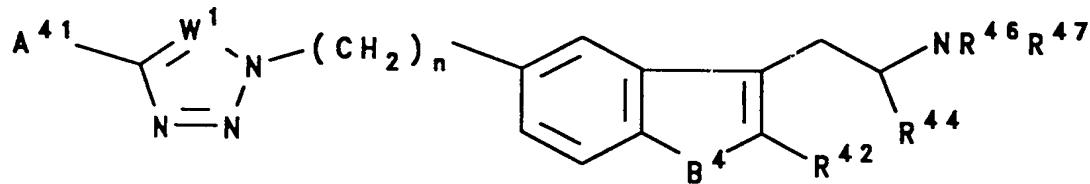
Examples of optional substituents on the groups A³¹ and A³² correspond to those indicated for the groups A¹¹ and A¹² with respect to formula IIA above.

Particular values of A^{31} and A^{32} with respect to formula IIC include hydrogen and methyl.

Preferably, R^{32} , R^{33} and R^{34} each represents hydrogen. Preferred values of R^{36} and R^{37} include hydrogen and methyl.

5

A still further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:



(IID)

wherein

W^1 represents nitrogen or $C-R^{42}$;

20 n is zero, 1, 2 or 3;

B^4 represents oxygen, sulphur or $N-R^{43}$;

25 A^{41} and A^{42} independently represent C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C_{1-6} alkoxy, C_{1-6} alkylthio or $-NR^XRY$;

30 R^{42} , R^{43} , R^{44} , R^{46} and R^{47} independently represent hydrogen or C_{1-6} alkyl; and

R^X and R^Y independently represent hydrogen or hydrocarbon, or R^X and R^Y together represent a C_{2-6} alkylene group.

Examples of optional substituents on the groups A^{41} and A^{42} correspond to those indicated for the groups

A^{11} and A^{12} with respect to formula IIA above.

Particular values of A^{41} and A^{42} with respect to formula IID include hydrogen and methyl.

Preferably, R^{42} , R^{43} and R^{44} each represents 5 hydrogen. Preferred values of R^{46} and R^{47} include hydrogen and methyl.

Specific compounds within the scope of the present invention include:

- 2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-
10 yl]ethylamine;
- 2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-
yl]ethylamine;
- N,N-dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-
15 3-yl]ethylamine;
- N,N-dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-
3-yl]ethylamine;
- N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-
20 yl]ethylamine;
- N,N-dimethyl-2-[5-(tetrazol-2-ylmethyl)-1H-indol-3-
yl]ethylamine;
- N,N-dimethyl-2-[5-(tetrazol-1-ylmethyl)-1H-indol-3-
25 yl]ethylamine;
- N,N-dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-
indol-3-yl]ethylamine;
- N,N-dimethyl-2-[5-(1-methyl-1,2,4-triazol-3-ylmethyl)-1H-
30 indol-3-yl]ethylamine;
- 3-(2-aminoethyl)-5-(1-methyltetrazol-5-yl)-
benzo[b]thiophene;
- 3-(2-aminoethyl)-5-(2-methyltetrazol-5-yl)-
benzo[b]thiophene;
- 3-[2-(N,N-dimethylamino)ethyl]-5-(2-methyltetrazol-5-
yl)benzo[b]thiophene;

N,N-dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

N,N-dimethyl-2-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

5 N,N-dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine;

and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, or suppositories, for oral, parenteral or

10 rectal administration. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium

15 stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When

20 referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then

25 subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise

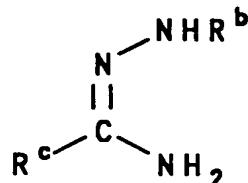
compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

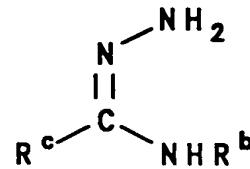
In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The 1,2,4-triazole compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula

$R^a\text{-CO}_2\text{H}$ with a compound either of formula III or of formula IV, or a salt thereof:



(III)



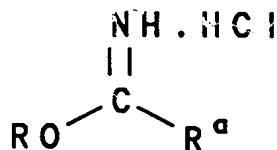
(IV)

wherein one of R^a , R^b and R^c is a group of formula A^1 , another is a group of formula A^2 , and the third is a group of formula $-E-F$, as defined with reference to formula I above.

15 Suitable reactive derivatives of the acid $R^a\text{-CO}_2\text{H}$ include esters, for example C_{1-4} alkyl esters; thioesters, for example pyridylthioesters; acid anhydrides, for example $(R^a\text{-CO})_2\text{O}$; acid halides, for example acid chlorides; orthoesters; and primary, secondary and tertiary amides.

20

A preferred reactive derivative of the acid $R^a\text{-CO}_2\text{H}$ is the iminoether derivative of formula V:



(V)

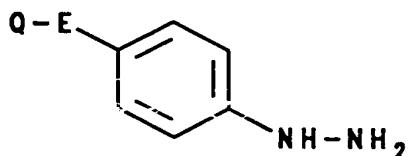
30 where R is C_{1-4} alkyl.

The reagent of formula III may be generated in situ in the reaction mixture. For example, the reaction may be effected by treating a compound of formula V above

with an alkyl hydrazine, e.g. methyl hydrazine, followed by a suitable carboxylic acid such as formic acid.

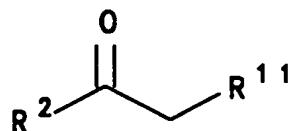
The reaction is conveniently carried out by heating the reagents together, optionally in a solvent, for example tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol, at about 20°C to 100°C for about 1 to 6 hours.

Where R^a is a group of formula -E-F and the group F is an indole moiety of structure FC as defined above, the reactive derivative of a carboxylic acid of formula HO_2C-E-F may be prepared by reacting a compound of formula VI:



(VI)

wherein Q represents a reactive carboxylate moiety, and E is as defined above; with a compound of formula VII or a carbonyl-protected form thereof:



(VII)

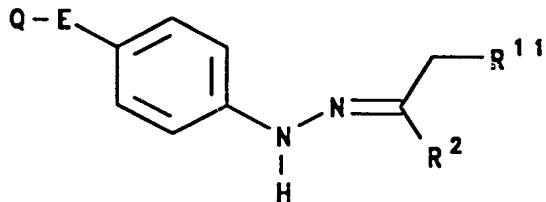
wherein R² is as defined above and R¹¹ corresponds to the group R¹ as defined above or represents a group of formula -CH₂.CHR⁴D¹, in which R⁴ is as defined above and D¹ represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

Suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal or ketal derivatives.

The readily displaceable group D¹ in the 5 compounds of formula VII suitably represents a halogen atom, preferably chlorine. When the moiety R¹¹ in the compounds of formula VII is a group of formula -CH₂.CHR⁴D¹, the substituent D¹ is displaced in situ under the prevailing reaction conditions to afford a 10 final product of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂. The terminal amino group can subsequently, if desired, be further elaborated using techniques known from the art to give a compound of formula I wherein R¹ represents the required group of 15 formula -CH₂.CHR⁴.NR⁶R⁷.

The reaction of compounds VI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:

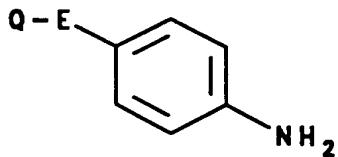
20



(VIII)

wherein Q, E, R² and R¹¹ are as defined above; followed by cyclisation using a suitable reagent, such as a 30 polyphosphate ester, to give a compound of formula Q-E-F.

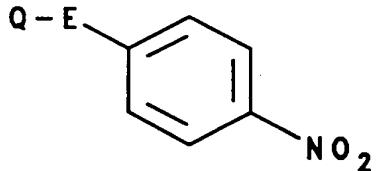
The hydrazines of formula VI may be prepared from the corresponding anilines of formula IX:



(IX)

wherein Q and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced in situ using, for example, tin(II) chloride/conc. HCl or sodium sulphite/conc. HCl.

The anilines of formula IX may be prepared by reduction of the corresponding nitro compounds of formula X:

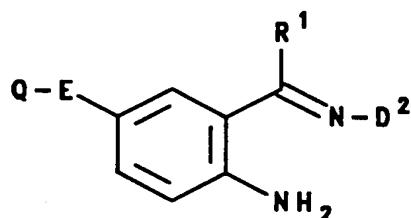


(X)

wherein Q and E are as defined above; typically by catalytic hydrogenation or using tin(II) chloride.

Where they are not commercially available, the nitro compounds of formula X may be synthesized by standard methods well known to those skilled in the art.

Where R^a is a group of formula -E-F and the group F is an indazole moiety of structure FB as defined above, the reactive derivative of a carboxylic acid of formula HO₂C-E-F may be prepared by the cyclisation of a compound of formula XI:

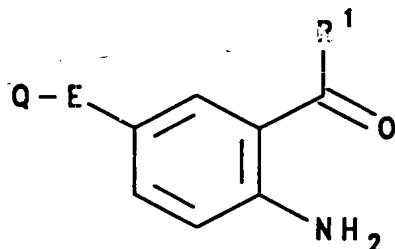


(XI)

wherein Q, E and R¹ are as defined above; and D²
10 represents a readily displaceable group; followed, where
required, by N-alkylation by standard methods to
introduce the moiety R³.

The cyclisation of compound XI is conveniently
achieved in a suitable organic solvent at an elevated
15 temperature, for example in a mixture of m-xylene and
2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D² in the
compounds of formula XI suitably represents a C₁₋₄
20 alkanoyloxy group, preferably acetoxy. Where D² in the
desired compound of formula XI represents acetoxy, this
compound may be conveniently prepared by treating a
carbonyl compound of formula XII:

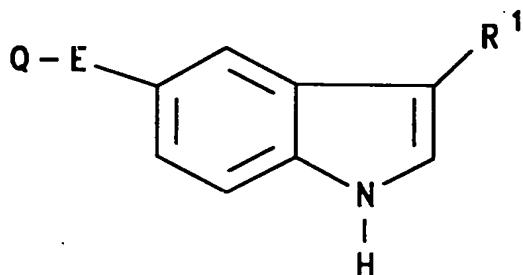


(XII)

wherein R¹, E and Q are as defined above; or a protected
derivative thereof; with hydroxylamine hydrochloride,
advantageously in pyridine at the reflux temperature of

the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

- 5 The N-formyl protected derivative of the intermediate of formula XII may be conveniently prepared by ozonolysis of an indole derivative of formula XIII:

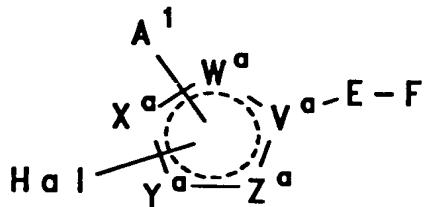


(XIII)

wherein R¹, E and Q are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

- 20 The indole derivative of formula XIII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

- 25 In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula XIV:



(XIV)

10 wherein A^1 , E and F are as defined above, Hal represents halogen, and two of V^a , W^a , X^a , Y^a and Z^a , to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent which provides an anion $^{-}A^2$, where A^2 is as previously defined.

15 Reagents which may provide the anion $^{-}A^2$ include Grignard reagents A^2MgHal (where Hal = halogen); organocuprate reagents such as LiA^2_2Cu ; organolithium reagents A^2Li ; or compounds which stabilise the anion by means of an adjacent activating group such as an ester or enolisable ketone function. In this case, the adjacent ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.

20 The 1,2,3-triazole compounds according to the present invention may be prepared by a process which comprises the cycloaddition of an alkyne of formula $R^a-C\equiv C-R^b$ with an azide of formula R^c-N_3 , where R^a , R^b and R^c are as defined above.

25 The cycloaddition reaction may be conveniently effected in a suitable solvent such as tetrahydrofuran, ideally by heating in an autoclave for 8 hours.

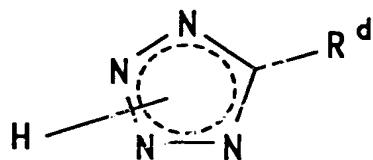
The tetrazole compounds in accordance with the invention may be prepared by a process which comprises the cycloaddition of a nitrile of formula $N\equiv C-R^d$ with an

azide of formula R^e-N_3 , where one of R^d and R^e represents a group of formula A^1 and the other is a group of formula $-E-F$, as defined previously.

The cycloaddition reaction is conveniently effected by heating the reactants together at an elevated temperature, e.g. a temperature in the region of $150^\circ C$, in a suitable solvent such as N-methylpyrrolid-2-one, advantageously in the presence of triethylamine hydrochloride. The product obtained from the cycloaddition reaction will generally be a mixture of isomers substituted by the A^1 group at positions 1 and 2 of the tetrazole ring, corresponding to structures IL and IM respectively as defined above. These isomers may conveniently be separated using conventional techniques such as chromatography.

In an alternative process, the tetrazole compounds of the invention may be prepared by a method which comprises reacting a compound of formula R^e-L with a tetrazole derivative of formula XV:

20



(XV)

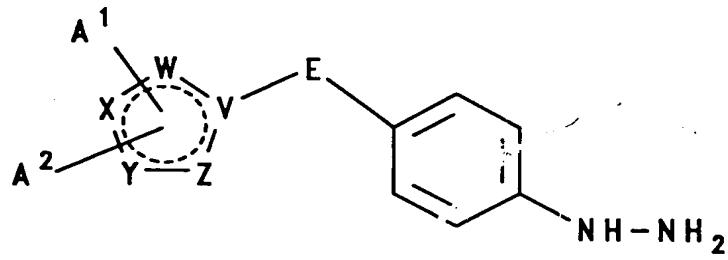
wherein one of R^d and R^e represents a group of formula A^1 and the other is a group of formula $-E-F$, as defined above, and L represents a suitable leaving group; in the presence of a base such as triethylamine.

The leaving group L suitably represents halogen, e.g. bromine or iodine, or a sulphonate derivative such as tosylate or mesylate.

The reaction is conveniently carried out in a suitable organic solvent, e.g. acetonitrile, at room temperature.

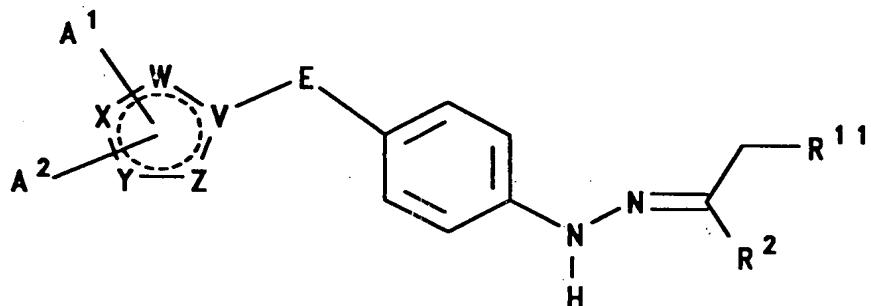
5 The tetrazole derivatives of formula XV may be prepared by cycloaddition of a nitrile of formula $N\equiv C-R^d$ with sodium azide, advantageously under the conditions described above for the reaction between the nitrile $N\equiv C-R^d$ and the azide R^e-N_3 ; followed by acidification with a mineral acid such as hydrochloric acid.

10 In a further process, the compounds according to the invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a method which comprises reacting a compound of formula XVI:



wherein V, W, X, Y, Z, A^1 , A^2 and E are as defined above; with a compound of formula VII as defined above, or a carbonyl-protected form thereof, e.g. the dimethyl acetal or ketal; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3 .

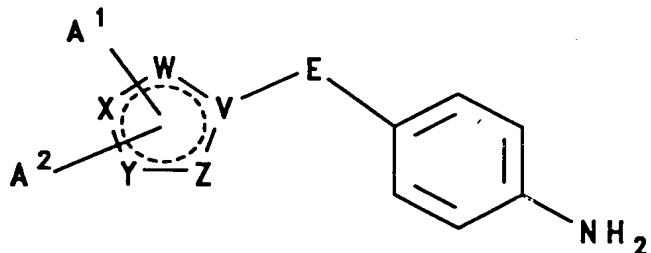
25 As with that between compounds VI and VII, the reaction between compounds XVI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XVII:



(XVII)

wherein V, W, X, Y, Z, A¹, A², E, R² and R¹¹ are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

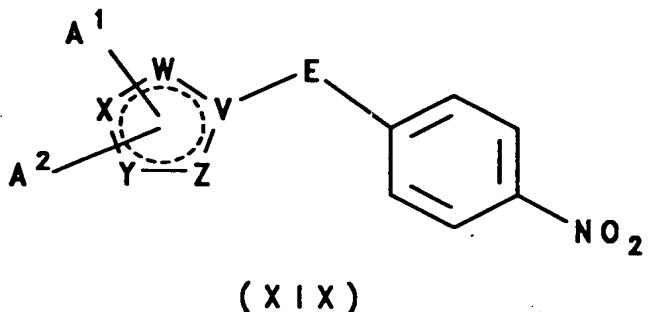
The hydrazines of formula XVI may be prepared
from the corresponding anilines of formula XVIII:



(XVIII)

wherein V, W, X, Y, Z, A¹, A² and E are as defined above;
by methods analogous to those described above with
reference to the compounds of formula IX.

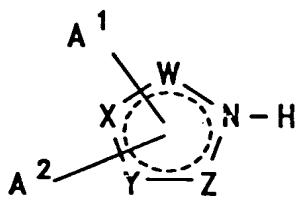
The anilines of formula XVIII may be prepared
from the corresponding nitro compounds of formula XIX:



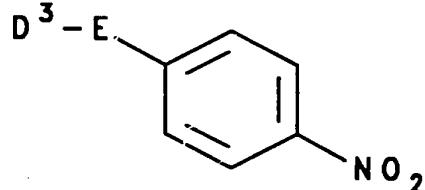
(XIX)

wherein V, W, X, Y, Z, A¹, A² and E are as defined above;
10 by methods analogous to those described above with
reference to the compounds of formula X.

The nitro compounds of formula XIX may be prepared by a variety of methods which will be readily apparent to those skilled in the art. For example, where
15 V represents a nitrogen atom, the relevant compounds of formula XIX may be prepared by reacting the anion of a compound of formula XX with a compound of formula XXI:



(XX)



(XXI)

wherein W, X, Y, Z, A¹, A² and E are as defined above,
and D³ represents a readily displaceable group.

Where compound XX is a triazole or tetrazole derivative, the anion thereof may be generated by carrying out the reaction in a base such as triethylamine. Where compound XX is an imidazole derivative, the anion thereof may conveniently be generated if the reaction is carried out in sodium hydride using N,N-dimethylformamide as solvent. Where
30

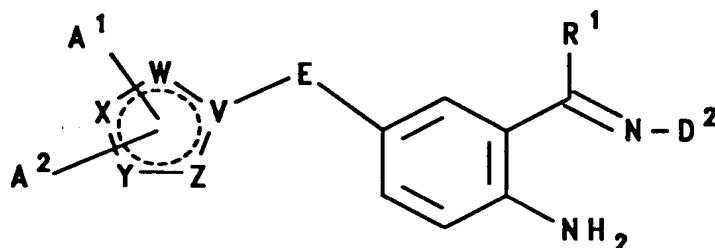
salts of the compounds of formula XX are commercially available, e.g. the sodium salt of 1,2,4-triazole, these are advantageously utilised in N,N-dimethylformamide solution in place of the compounds of formula XX themselves, with no requirement in this instance for additional base to be present in the reaction mixture.

The readily displaceable group D³ in the compounds of formula XXI is suitably a halogen atom, preferably bromine; except when the moiety D³ is attached directly to the aromatic ring, i.e. when E represents a bond, in which case D³ is preferably fluorine.

Where they are not commercially available, the nitro compounds of formula XXI above may be prepared by procedures analogous to those described in the accompanying Examples, or by methods well known from the art.

In an alternative approach to the 1,2,4-triazole derivatives, the nitro compounds of formula XIX may be prepared from those of formula X above by appropriate modification of the moiety Q using, for example, methods analogous to those described above with reference to the compounds of formulae III and IV. Thus, for example, since Q in the compounds of formula X represents a reactive carboxylate moiety, the compounds of formula XIX may be prepared therefrom by reaction with a compound of formula A²-C(=NNH¹)NH₂ or A²-C(=NNH₂)NHA¹.

In a still further process, the compounds according to the invention wherein the group F is an imidazole moiety of structure FB as defined above may be prepared by a method which comprises cyclising a compound of formula XXII:



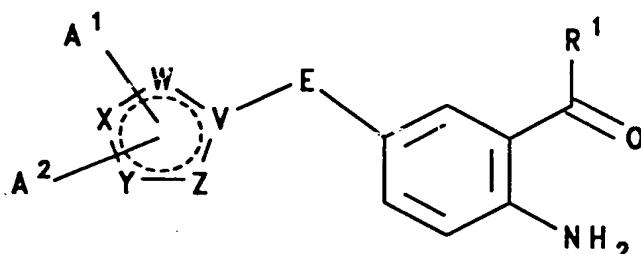
(XXII)

wherein V, W, X, Y, Z, A¹, A², E, R¹ and D² are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

As with the cyclisation of compound XI, that of compound XXII is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The compounds of formula XXII may, for example, be prepared from the corresponding compound of formula XXIII:

20

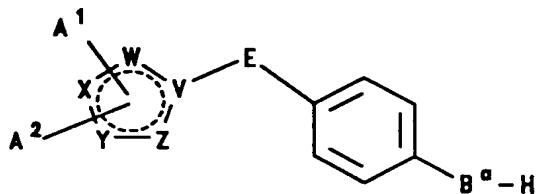


(XXIII)

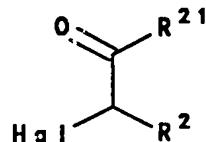
wherein V, W, X, Y, Z, A¹, A², E and R¹ are as defined above; or a protected derivative thereof; which in turn may be prepared from the corresponding compound of formula XXIV:

The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

5 The compounds of formula XXV may be prepared by reacting a compound of formula XXVI with a compound of formula XXVII:



(XXVI)



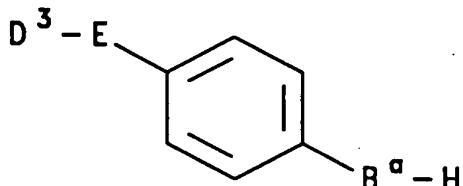
(XXVII)

15 wherein V, W, X, Y, Z, A¹, A², E, B^a, R² and R²¹ are as defined above, and Hal represents halogen.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

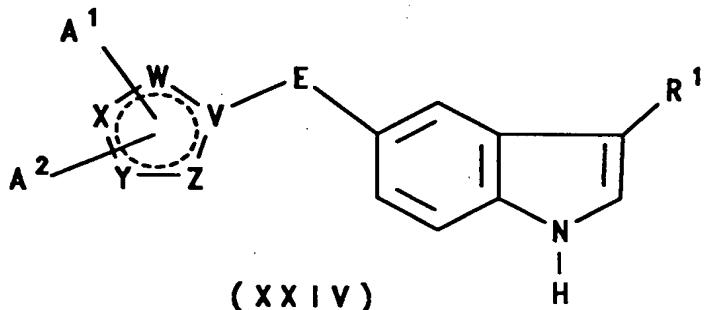
20 The hydroxy and mercapto derivatives of formula XXVI may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, the anion of a compound of formula XX as defined above is reacted with a compound of formula XXVIII:

25



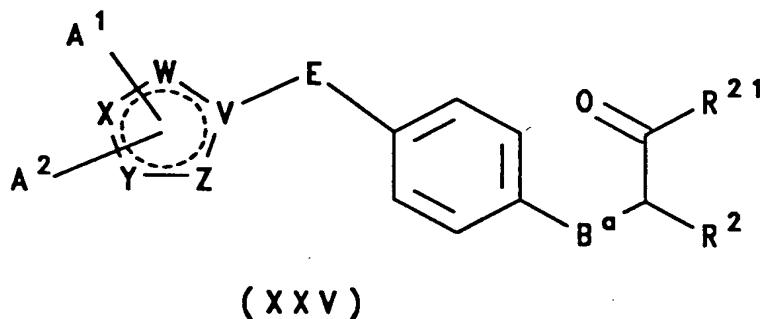
(XXVIII)

wherein D³, E and B^a are as defined above; to afford an intermediate of formula XXVI wherein V is nitrogen.



wherein V, W, X, Y, Z, A¹, A², E and R¹ are as defined above; using methods analogous to those described above with reference to the compounds of formulae XII and XIII. Thus, for example, since Q in the compounds of formula XIII represents a reactive carboxylate moiety, the 1,2,4-triazole derivatives of formula XXIV may be prepared therefrom by reaction with a compound of formula A²-C(=NNHA¹);NH₂ or A²-C(=NNH₂)NHA¹.

In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a method which comprises cyclising a compound of formula XXV:



wherein V, W, X, Y, Z, A¹, A², E and R² are as defined above; B^a represents oxygen or sulphur; and R²¹ corresponds to the group R¹ as defined above, or represents a precursor group thereto as discussed below.

The compounds of formula XXVII and XXVIII, where they are not commercially available, may be prepared by standard procedures well known in the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. Indeed, as will be appreciated, the compound of formula XV above in which R^d 5 is a group of formula -E-F is itself a compound of formula I in which A¹ is hydrogen and A² represents a non-bonded electron pair. In particular, a compound of formula I wherein R³ is hydrogen initially obtained may 10 be converted into a compound of formula I wherein R³ represents C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl by 15 standard techniques such as alkylation, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile. 20 Similarly, a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NH₂ initially obtained may be converted into a compound of formula I wherein R¹ represents a group of formula -CH₂.CHR⁴.NR⁶R⁷ in which R⁶ 25 and R⁷ are as defined above with the exception of hydrogen, for example by conventional N-alkylation or N-arylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent such as sodium cyanoborohydride.

Where the above-described processes for the 30 preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1981. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Alternatively, certain of the functional groups on the desired products may be carried through the reaction sequence as precursor groups, and then regenerated from these precursor groups at a late stage in the overall synthesis. For example, where R¹ in the desired compound of formula I represents a group of formula -(CH₂)₂NH₂, this group can be generated from a cyano precursor -CH₂CN by reduction using, for example, borane/tetrahydrofuran. The cyano precursor may in turn be carried through the reaction sequence as a methyl group -CH₃, which may conveniently be converted to -CH₂CN.

by treatment with N-bromosuccinimide and benzoyl peroxide, in the presence of a bright light source, followed by reaction of the resulting bromo intermediate with sodium cyanide in dimethyl sulphoxide.

5 The following Examples illustrate the preparation of compounds according to the invention.

The ability of test compounds to bind to 5-HT₁-like receptors was measured in membranes prepared from pig caudate using the procedure described in
10 J. Neurosci., 1987, 7, 894. Binding was determined using 2 nM 5-hydroxytryptamine creatinine sulphate, 5-[1,2-³H(N)] as a radioligand. Cyanopindolol (100 nM) and mesulergine (100 nM) were included in the assay to block out 5-HT_{1A} and 5-HT_{1C} binding sites respectively.
15 The concentration of the compounds of the accompanying Examples required to displace 50% of the specific binding (IC₅₀) is below 1 μM in each case.

The activity of test compounds as agonists of the 5-HT₁-like receptor was measured in terms of their ability to mediate contraction of the saphenous vein of New Zealand White rabbits, using the procedure described in Arch. Pharm., 1990, 342, 111. Agonist potencies were calculated as -log₁₀EC₅₀ (pEC₅₀) values, from plots of percentage 5-HT (1 μM) response against the concentration of the agonist. The compounds of the accompanying Examples were found to possess pEC₅₀ values in this assay of not less than 5.0 in each case.

EXAMPLE 1

2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

5

1. 4-Hydrazinobenzylcyanide. Hydrochloride

A solution of NaNO₂ (80g, 1.16mol) was added dropwise to a cooled (-10°C), stirred, suspension of 4-aminobenzyl cyanide (153.5g, 1.16mol) in concentrated HCl (1500ml), at such a rate that the temperature did not rise above -10°C. The mixture was stirred at -10°C for 0.25h before being filtered rapidly under vacuum into an addition funnel. The solution was added portionwise over a 0.25h period to a rapidly stirred mixture of SnCl₂.2H₂O (1.05kg, 4.64mol) in concentrated HCl (800ml) keeping the temperature below -5°C. The mixture was allowed to warm to room temperature and stir for 0.25h before filtering the sandy coloured precipitate under vacuum and washing with ether (5 x 500ml). The resultant solid was dried over P₂O₅ in a vacuum oven (80°C) for 16h to give the title compound (213g, 100%), m.p. 181-183°C; ¹H NMR (360MHz, D₂O) δ 3.90 (2H, s, CH₂); 7.06 (2H, d, J = 8.7Hz, Ar-H); 7.40 (2H, d, J = 8.7Hz, Ar-H).

2. 2-(5-Cyanomethyl-1H-indol-3-yl)ethylamine Hydrochloride

5 4-Chlorobutanal dimethylacetal (37.07g, 0.24mol) was added to a stirred solution of 4-hydrazinobenzyl cyanide hydrochloride (47.0g, 0.26mol) in EtOH/H₂O (5:1; 21) and refluxed for 4.5h. The reaction mixture was evaporated to dryness under vacuum, MeOH (150ml) added, and the mixture left at 0°C for 10h. The resultant pale yellow precipitate was
10 filtered under vacuum, washed with Et₂O/MeOH (5:1; 2 x 100ml) and dried. The product was used without further purification (24.1g, 40%), m.p. 239-241°C; R_f 0.4 in CH₂Cl₂/EtOH/NH₃ (40:8:1); ¹H NMR (360MHz, D₂O) 3.18 (2H, t, J = 7.1Hz, CH₂); 3.36 (2H, t, J = 7.1Hz, CH₂); 4.02 (2H, s, CH₂); 7.22 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H);
15 7.56 (1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

3. 2-(5-Tetrazol-5-ylmethyl-1H-indol-3-yl) ethylamine

20 A solution of 2-(5-cyanomethyl-1H-indol-3-yl)ethylamine hydrochloride (2.5g, 10.6mmol), triethylamine hydrochloride (2.2g, 16.0mmol) and sodium azide (2.1g, 32.3mmol), in 1-methylpyrrolidin-2-one (30ml) was heated at 140°C for 8h. 5N hydrochloric acid (3ml) was added and the solvents removed by distillation under vacuum. The residue was chromatographed on silica-gel eluting with EtOH/Et₂O/H₂O/NH₃ (20:30:8:1) to give the title-tetrazole (1.76g, 69%); δ (360MHz, CD₃OD) 3.06 (2H, t, J = 7.2Hz, CH₂); 3.19 (2H, t, J = 7.2Hz, CH₂); 4.29 (2H, s,

CH₂); 7.07 (1H, d, J = 8.4Hz, Ar-H); 7.13 (1H, s, Ar-H); 7.29 (1H, d, J = 8.4Hz, Ar-H); 7.44 (1H, s, Ar-H).

5 4. N-tert-Butyloxycarbonyl-2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine

To a stirred suspension of 2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine (1.76g, 7.27mmol) in dry CH₂Cl₂ (40ml) was added triethylamine (1.5g, 14.9mmol) and (BOC)₂O (1.9g, 7.3mmol) and the mixture stirred for 16h. The solvent was removed under vacuum and the residue chromatographed on silica-gel eluting with EtOH/Et₂O/H₂O/NH₃ (20:60:8:1) to give the title product (1.6g, 64%); δ (360MHz, CD₃OD) 1.41 (9H, s, 3 of CH₃); 2.87 (2H, t, J = 7.4Hz, CH₂); 3.30 (2H, t, J = 7.4Hz, CH₂); 4.32 (2H, s, CH₂); 6.99 (1H, d, J = 8.3Hz, Ar-H); 7.04 (1H, s, Ar-H); 7.26 (1H, d, J = 8.3Hz, Ar-H); 7.49 (1H, s, Ar-H).

10 15 20 5. N-tert-Butyloxycarbonyl-2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and N-tert-butyloxycarbonyl-2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

Benzyl bromide (0.31g, 1.8mmol) was added to a solution of the tetrazole from step 4 (0.62g, 1.8mmol), and triethylamine (0.37g, 3.6mmol) in dry acetonitrile (20ml). The mixture was stirred at R.T. for 2h, heated at 70°C for 1h and then stirred at

R.T. for 16h. The solvent was removed under vacuum and the residue chromatographed through silica-gel eluting with CH₂Cl₂/MeOH (97:3) to give 2-separated benzyl tetrazoles. The less polar isomer was identified as the 2-benzyl tetrazole (0.17g, 22.4%); δ (360MHz, CDCl₃) 1.43 (9H, s, 3 of CH₃); 2.90 (2H, t, J = 6.8Hz, CH₂); 3.41 (2H, br t, CH₂); 4.32 (2H, s, CH₂); 5.70 (2H, s, CH₂Ph); 7.00 (1H, s, Ar-H); 7.15 (1H, d, J = 8.4Hz, Ar-H); 7.28 (1H, d, J = 8.4Hz, Ar-H); 7.34 (5H, s, Ar-H); 7.50 (1H, s, Ar-H); 7.96 (1H, br s, NH).

10

The more polar component was identified as the 1-benzyltetrazole (0.2g, 26.4%) δ (360MHz, CDCl₃) 1.43 (9H, s, 3 of CH₃); 2.88 (2H, t, J = 7.0Hz, CH₂); 3.40 (1H, br t, CH₂); 4.26 (2H, s, CH₂); 5.29 (2H, s, CH₂-Ph); 6.92 (1H, d, J = 8.4Hz, Ar-H); 7.01-7.05 (3H, m, Ar-H); 7.27-7.30 (5H, m, Ar-H); 8.08 (1H, br s, NH).

15

6. 2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

20

Trifluoroacetic acid (1.5ml) was added to a solution of the less polar component isolated from step 5 (0.17g, 0.4mmol) in CH₂Cl₂ (5ml) and stirred at R.T. for 1h. The solvents were removed under vacuum and the residue chromatographed through silica-gel eluting with CH₂Cl₂/EtOH/NH₃ (40:8:1) to give the title-tetrazole. The oxalate salt was prepared (65mg); mp 169-171°C; (Found: C, 59.23; H, 5.07; N, 19.60.

C₁₉H₂₀N₆.1.05 (C₂H₂O₄) requires C, 59.36; H, 5.22; N, 19.68%; δ (360MHz, D₂O) 3.09 (2H, t, J = 6.9Hz, CH₂); 3.29 (2H, t, J = 6.9Hz, CH₂); 4.30 (2H, s, CH₂); 5.77 (2H, s, CH₂); 7.11 (1H, dd, J = 1.6 and 8.4Hz, Ar-H); 7.28 (1H, s, Ar-H); 7.32-7.34 and 7.39-7.41 (5H, m, Ar-H); 7.43 (1H, d, J = 8.4Hz, Ar-H); 7.51 (1H, s, Ar-H).

5

EXAMPLE 2

10

2-[5-(1-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Hydrochloride. Hemihydrate

15

Prepared from the more polar component isolated from step 5, Example 1, using the procedure described for step 6, Example 1. The hydrochloride hemihydrate salt was prepared; mp 210-213°C; (Found: C, 60.39; H, 5.88; N, 22.14. C₁₉H₂₀N₆.HCl.0.5H₂O requires C, 60.39; H, 5.87; N, 22.24%); δ (250MHz, D₂O) 3.02 (2H, t, J = 6.8Hz, CH₂); 3.19 (2H, t, J = 6.8Hz, CH₂); 4.44 (2H, s, CH₂); 5.30 (2H, s, CH₂); 6.95-7.02 (3H, m, Ar-H); 7.16-7.25 (4H, m, Ar-H); 7.28 (1H, s, Ar-H); 7.40 (1H, d, J = 8.4Hz, Ar-H).

20

EXAMPLE 3

25

N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

1. N-tert-Butyloxycarbonyl-2-[5-(2-methyltetrazol-5-

y1methyl)-1H-indol-3-yl]ethylamine and N-tert-
butyloxycarbonyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-
yl]ethylamine

5 Methyl iodide (0.44g, 3.1mmol) was added to a stirred solution of the tetrazole from step 4, Example 1 (0.95g, 2.78mmol) and triethylamine (0.56g, 5.5mmol) in dry acetonitrile (15ml). After 10h a further equivalent of methyl iodide was added and stirred for 16h. The solvent was removed
10 under vacuum and the residue chromatographed on silica-gel eluting with CH₂Cl₂/MeOH (97:3) to give the title mixture of 1- and 2-methyltetrazoles (0.6g, 61%); δ (360MHz, CDCl₃) 1.43 (9H, m, 3 of CH₃); 2.89-2.92 (2H, m, CH₂); 3.38-3.48 (2H, m, CH₂); 3.83 (2H, s, CH₂); 4.28 and 4.40 (total 3H, s, CH₃); 6.98 and 7.17 (total 1H, d, J = 8.4Hz, Ar-H); 7.02 and 7.06 (total 1H, s, Ar-H); 7.30 and 7.31 (total 1H, d, J = 8.4Hz, Ar-H); 7.43 and 15 7.54 (total 1H, s, Ar-H); 8.00 and 8.10 (total 1H, br s, NH).

20 2. 2-[5-(2-Methyltetrazol-5-ylmethyl)-1H-indol-3-
yl]ethylamine and 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-
3-yl]ethylamine

25 Prepared from the preceding methyltetrazoles using the procedure described in step 6, Example 1. The crude product was chromatographed on silica-gel eluting with CH₂Cl₂/EtOH/NH₃ (40:8:1) to give 2 separated components. The less polar product (0.1g, 24%) was identified as the 2-

methyltetrazole; δ (360MHz, CDCl₃) 1.38 (9H, s, 3 of CH₃); 2.88 (2H, t, J = 6.6Hz, CH₂); 3.00 (2H, t, J = 6.6Hz, CH₂); 4.28 (3H, s, CH₃); 4.33 (2H, s, CH₂); 7.00 (1H, d, J = 8.4Hz, Ar-H); 7.06 (1H, d, J = 2.1Hz, Ar-H); 7.17 (1H, d, J = 8.4Hz, Ar-H); 7.56 (1H, s, Ar-H); 8.04 (1H, br s, NH).

5

The more polar product (0.13g, 31%) was identified as the 1-methyltetrazole; δ (360MHz, CDCl₃) 1.38 (9H, s, 3 of CH₃); 2.86 (2H, t, J = 6.6Hz, CH₂); 3.00 (2H, t, J = 6.6Hz, CH₂); 3.82 (3H, s, CH₃); 4.40 (2H, s, CH₂); 6.98 (1H, dd, J = 1.6 and 8.3Hz, Ar-H); 7.06 (1H, d, J = 1.6Hz, Ar-H); 7.31 (1H, d, J = 8.3Hz, Ar-H); 7.41 (1H, s, Ar-H); 8.18 (1H, br s, NH).

10

3. N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

15

20

25

A solution of formaldehyde (80mg of a 30% solution) in methanol (15ml) was added to a stirred solution of 2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.1g, 0.4mmol), NaCNBH₃ (60mg) and glacial acetic acid (0.12g) in methanol (15ml). The solution was stirred for 2h, basified with K₂CO₃ solution and the MeOH removed under vacuum. The crude product obtained after extraction into ethylacetate and removal of solvent was chromatographed through silica-gel eluting with CH₂Cl₂/EtOH/NH₃ (40:8:1) to give the desired N,N-dimethyltryptamine (96mg, 87%). The oxalate salt was prepared: mp 185-187°C (MeOH/Et₂O); (Found: C, 54.42; H,

5.74; N, 22.53. $C_{15}H_{20}N_6 \cdot C_2H_2O_4$ requires C, 54.54; H, 5.92; N, 22.45%); δ (360MHz, D_2O) 2.91 (6H, s, 2 of CH_3); 3.21 (2H, t, $J = 7.4$ Hz, CH_2); 3.47 (2H, t, $J = 7.4$ Hz, CH_2); 4.30 (3H, s, CH_3); 4.34 (2H, s, CH_2); 7.17 (1H, dd, $J = 1.5$ and 8.4Hz, Ar-H); 7.33 (1H, s, Ar-H); 7.48 (1H, d, $J = 8.4$ Hz, Ar-H); 7.59 (1H, s, Ar-H).

EXAMPLE 4

10 N,N-Dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

15 Prepared from 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.125g, 0.49mmol) using the procedure described in step 3, Example 3. The free base (0.11g, 80%) obtained was converted to the oxalate salt and recrystallised from MeOH/Et₂O; mp 176-177°C; (Found: C, 54.21; H, 5.84; N, 22.36. $C_{15}H_{20}N_6 \cdot C_2H_2O_4$ requires C, 54.54; H, 5.92; N, 22.45%); δ (360MHz, D_2O); 2.91 (6H, s, 2 of CH_3); 3.21 (2H, t, $J = 7.4$ Hz, CH_2); 3.40 (2H, t, $J = 7.4$ Hz, CH_2); 4.00 (3H, s, CH_3); 4.43 (2H, s, CH_2); 7.13 (1H, dd, $J = 1.5$ and 8.4Hz, Ar-H); 7.35 (1H, s, Ar-H); 7.50 (1H, d, $J = 3.4$ Hz, Ar-H); 7.54 (1H, s, Ar-H).

EXAMPLE 5

25 N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate Hemihydrate

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

4-Nitrobenzylbromide (21.6g, 0.1mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1g, 0.1mol) in anhydrous DMF (100ml) and the mixture stirred at room temperature for 16h. Ethyl acetate (400ml) was added followed by water (250ml) and the layers separated. The organic phase was washed with water (3 x 250ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate to give the title-product (10.6g, 52%); m.p. 98-100°C. δ (360MHz, $CDCl_3$) 5.47 (2H, s, CH_2) 7.40 (2H, d, J = 9Hz, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 8.23 (2H, d, J = 9Hz, Ar-H).

2. 1-(4-Aminophenyl)methyl-1,2,4-triazole. Hydrochloride

A solution of 1-(4-nitrophenyl)methyl-1,2,4-triazole (10.0g, 49mmol) in ethanol (50ml), ethyl acetate (50ml), 5N HCl (10ml) and water (10ml) was hydrogenated over 10% Pd/C (1.0g) at 40 p.s.i., in a Parr apparatus, until an uptake of 188 p.s.i., had been observed (approx 10mins). The catalyst was removed by filtration through hyflo and the solvent removed under vacuum. The residue was azeotroped with ethanol (x2) to give the title-amine hydrochloride (10.6g, 100%). δ (360MHz, D_2O) 5.53 (2H, s, CH_2), 7.37-7.48 (4H, m, Ar-H), 8.12 (1H, s, Ar-H), 8.66 (1H, s, Ar-H).

3. 1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

A solution of sodium nitrite (3.28g, 48mmol) in water (20ml) was added to a solution of the preceding amine hydrochloride (10.0g, 48mmol), in concentrated HCl (40ml), at such a rate that the temperature did not exceed -10°C. After addition was complete the solution was stirred at 0°C for 0.25h and then added portionwise to a rapidly stirred solution of SnCl₂.2H₂O (40g) in concentrated HCl (40ml). The solution was warmed to room temperature and basified with 20% aqueous NaOH solution. The solution was extracted with ethyl acetate (3 x 250ml) and the combined extracts dried (MgSO₄) and filtered through hyflo. The solution was evaporated to dryness to give the desired hydrazine (5.0g, 56%) m.p. 109-112°C. δ (360MHz, D₆-DMSO) 3.93 (2H, br s, NH₂), 5.20 (2H, s, CH₂), 6.73 (2H, d, J = 8Hz, Ar-H), 7.08 (2H, d, J = 8Hz, Ar-H), 7.92 (1H, s, Ar-H), 8.57 (1H, s, Ar-H).

4. 2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine.

4-Chlorobutanal dimethylacetal (3.22g, 21.1mmol) was added to a stirred solution of the preceding hydrazine (5.0g, 26.4mmol) in ethanol/water (5:1, 180ml) and 5N HCl (4.5ml) and the solution refluxed for 4h. The solvents were removed under vacuum and the residue chromatographed on silica gel, eluting with CH₂Cl₂/EtOH/NH₃ (30:8:1) to give the desired tryptamine (2.4g, 38%). δ(360MHz, CDCl₃) 2.90 (2H, t, J = 7Hz,

CH₂), 2.99 (2H, t, J = 7Hz, CH₂), 5.43 (2H, s, CH₂), 7.10 (1H, s, Ar-H), 7.11 (1H, d, J = 8Hz, Ar-H), 7.39 (1H, d, J = 8Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.08 (1H, s, Ar-H).

5

5. N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate Hemihydrate

A solution of formaldehyde (37% w/w solution, 0.19g), in methanol (10ml), was added to a mixture of the preceding tryptamine (0.36g, 1.5mmol), NaCNBH₃ (0.225g, 3.6mmol) and glacial acetic acid (0.45g), in methanol (10ml). The mixture was stirred at room temperature for 2h before adding saturated K₂CO₃ (50ml) and evaporating the methanol. The residue was extracted with ethyl acetate (3 x 100ml) and the combined extracts washed with brine (100ml), dried (K₂CO₃), and evaporated. The crude product was chromatographed on silica gel eluting with CH₂Cl₂/EtOH/NH₃ (20:8:1) to give the free base of the title-compound (0.21g, 52%). The oxalate hemihydrate salt was prepared, m.p. 165-167°C (MeOH/Et₂O); (Found: C, 55.53; H, 6.04; N, 18.59. C₁₅H₁₉N₅.C₂H₂O₄.0.55H₂O requires C, 55.29; H, 6.03; N, 18.96%); m/e 269 (M⁺); δ (360MHz, D₂O) 2.91 (6H, s, NMe₂), 3.22 (2H, t, J = 7Hz, CH₂), 3.47 (2H, t, J = 7Hz, CH₂), 5.52 (2H, s, CH₂), 7.21 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 7.65 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 8.56 (1H, s, Ar-H).

EXAMPLE 6

N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate.

5

1. 1-(4-Nitrophenyl)methyl-1,2,3,4-tetrazole and 2-(4-nitrophenyl)methyl-1,2,3,4-tetrazole.

10

4-Nitrobenzylbromide (15.42g, 71.3mmol) was added to a stirred solution of 1H-tetrazole (5.0g, 71.3mmol) and triethylamine (7.9g, 78.0mmol) in acetonitrile (100ml). The mixture was stirred at room temperature for 16h, the solvent removed under vacuum and the residue chromatographed on silica gel eluting with dichloromethane to give 2-isomers. The 2-alkylated product was obtained as the less polar product (2.47g, 17%); δ (360MHz, CDCl₃) 5.92 (2H, s, CH₂), 7.53 (2H, d, J = 8.7Hz, Ar-H), 8.25 (2H, d, J = 8.7Hz, Ar-H), 8.56 (1H, s, Ar-H). The more polar, major isomer was identified as the 1-alkylation product (11g, 75%); δ (360MHz, CDCl₃) 5.73 (2H, s, CH₂), 7.46 (2H, d, J = 8.7Hz, Ar-H), 8.27 (2H, d, J = 8.7Hz, Ar-H), 8.64 (1H, s, Ar-H).

20

2. 2-(4-Aminophenyl)methyl-1,2,3,4-tetrazole.
Hydrochloride

25

2-(4-Nitrophenyl)methyl-1,2,3,4-tetrazole (2.47g, 12.1mmol) was hydrogenated as described for Example 5 step 2. The product (2.55g, 100%) was obtained as the hydrochloride

salt; δ (250MHz, D₂O) 5.86 (2H, s, CH₂), 7.40 (2H, d, J = 8.7Hz, Ar-H), 7.36 (2H, d, J = 8.7Hz, Ar-H), 8.74 (1H, s, Ar-H).

5 3. N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

The preceding amine was converted into the title-compound using the general procedures described for Example 5 Steps 3-5. The oxalate salt was prepared and recrystallised from MeOH/Et₂O; mp 198-199°C; (Found: C, 53.38; H, 5.55; N, 22.63. C₁₄H₁₈N₆. C₂H₂O₄. 0.2 (EtOH) requires C, 53.30; H, 5.78; N, 22.74%); δ (360MHz, D₂O) 2.01 (6H, s, NMe₂), 2.23 (2H, t, J = 7.4Hz, CH₂), 3.48 (2H, t, J = 7.4Hz, CH₂), 6.01 (2H, s, CH₂), 7.30 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.53 (1H, d, J = 8.4Hz, Ar-H), 7.76 (1H, s, Ar-H), 8.74 (1H, s, Ar-H).

20 EXAMPLE 7

20 N,N-Dimethyl-2-[5-1,2,3,4-tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Succinate

25 1-(4-nitrophenyl)methyl-1,2,3,4-tetrazole was converted into the title-compound using the procedures described for Example 5. The succinate salt was prepared, m.p. 55-56°C (isopropylalcohol); (Found C: 57.08; H, 6.14; N, 23.34. C₁₄H₁₈N₆. 0.75 (C₄H₆O₄) requires C, 56.89; H, 6.32; N,

23.42%); δ (360MHz, D₂O) 2.93 (6H, s, NMe₂), 3.23 (2H, t, J = 7.5Hz, CH₂), 3.48 (2H, t, J = 7.5Hz, CH₂), 5.81 (2H, s, CH₂), 7.28 (1H, dd, J = 1.7 and 8.4Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.56 (1H, d, J = 8.4Hz, Ar-H), 7.75 (1H, s, Ar-H), 9.20 (1H, s, Ar-H).

5

EXAMPLE 8

N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Bisoxalate

10

1. Ethyl 3-[2-(dimethylamino)ethyl]-1H-indole-5-methylcarboximidate. Hydrochloride

15

A solution of N,N-dimethyl-2-(5-cyanomethyl-1H-indol-3-yl)ethylamine (5g, 22.01mmol) in ethanol was saturated with HCl gas and the solution stirred at room temperature for 16h. The solvent was removed under vacuum to give the title product (6g, 92%); δ (360MHz, D₆-DMSO) 1.29 (3H, t, J = 7.0Hz, CH₂); 2.83 (6H, s, NMe₂), 3.13 (2H, t, J = 7.5Hz, CH₂), 3.31 (2H, m, CH₂), 4.04 (2H, s, CH₂), 4.42 (2H, q, J = 7.0Hz, CH₂), 7.08 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.27 (1H, s, Ar-H), 7.37 (1H, d, J = 8.4Hz, Ar-H), 7.48 (1H, br s, NH), 7.71 (1H, s, Ar-H).

20

2. N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Bisoxalate

25

A mixture of the preceding imidate ester (3g, 10.15mmol), methylhydrazine (0.8ml) and triethylamine (3.54ml), in ethanol (30ml), was stirred at room temperature for 3h. The solvent was removed under vacuum and the resultant product dissolved in formic acid (98%, 3.3ml) and the solution stirred for 0.5h at room temperature and refluxed for 2h. The solution was cooled to room temperature, poured into an aqueous solution of K_2CO_3 (75ml) and extracted with ethyl acetate (4 x 200ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the residue chromatographed through silica gel eluting with $CH_2Cl_2/EtOH/NH_3$ (40:8:1) to give 2-components. The less polar isomer was identified as the title-1-methyl-1,2,4-triazole (360mg). The bisoxalate salt was prepared; mp 135-137°C; (Found: C, 50.91; H, 5.38; N, 13.86. $C_{16}H_{21}N_5$. 0.25(ethanol) requires C, 50.70; H, 5.47; N, 14.08%); δ (360MHz, D_2O) 2.91 (6H, s, NMe_2); 3.23 (2H, t, J = 7.3Hz, CH_2), 3.48 (2H, t, J = 7.3Hz, CH_2), 3.95 (3H, s, Me), 4.48 (2H, s, CH_2), 7.13 (1H, dd, J = 1.5 and 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.53 (1H, d, J = 8.4Hz, Ar-H), 7.57 (1H, s, Ar-H), 8.32 (1H, s, Ar-H).

20

EXAMPLE 9

N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-3-ylmethyl)-1H-indol-3-yl]ethylamine. Trishydrochloride

25

The more polar isomer obtained from Example 8 Step 2

was identified as the title-triazole (180mg). The trishydrochloride salt was prepared, mp <40°C (hygroscopic); Found: C, 49.80, H, 6.56; N, 16.69. $C_{16}H_{21}N_5 \cdot 3HCl$. 0.35 (Et₂O) requires C, 49.91; H, 6.62; N, 16.73%); δ (360MHz, D₂O) 2.91 (6H, s, NMe₂); 3.23 (2H, t, J = 7.4Hz, CH₂), 3.49 (2H, t, J = 7.4Hz, CH₂), 3.95 (3H, s, Me), 4.27 (2H, s, CH₂), 7.17 (1H, dd, J = 1.5 and 8.5Hz, Ar-H), 7.34 (1H, s, Ar-H), 7.50 (1H, d, J = 8.5Hz, Ar-H), 7.60 (1H, s, Ar-H), 8.88 (1H, s, Ar-H).

10

EXAMPLE 10

N,N-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

15

1. 1-(4-nitrophenyl)methyl-1,2,3-triazole

4-Nitrobenzylbromide (25.4g, 0.12mol) was added to a solution of 1H-1,2,3-triazole (8.12g, 0.12mol) and triethylamine (11.88g, 0.12mol) in anhydrous acetonitrile. The mixture was refluxed for 1h, cooled to room temperature and the precipitated NEt₃·HBr filtered off. The solvent was removed under vacuum and the residue chromatographed through silica gel eluting with CH₂Cl₂ (100) to CH₂Cl₂/MeOH (95.5) to give 2-products. The more polar product was identified as the title-1-isomer (13g, 54%); mp 114-116°C δ (250MHz, CDCl₃) 5.72 (2H, s, CH₂), 7.38 (2H, d, J = 9Hz, Ar-H), 7.64 (1H, s, Ar-H), 7.78 (1H, s, Ar-H), 8.18 (2H, d, J = 9Hz, Ar-H). The less polar, minor isomer was

identified as the 2-alkylation product (2.25g, 9%), mp 112-113°C.
δ (250MHz, CDCl₃) 5.72 (2H, s, CH₂), 7.40 (2H, d, J = 9Hz, Ar-H), 7.66 (2H, s, Ar-H), 8.18 (2H, d, J = 9Hz, Ar-H).

5

2. N,N-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

10 1-(4-nitrophenyl)methyl-1,2,3-triazole was converted into the title-indole using the general procedures described for example 5. The oxalate salt was prepared mp 210-212°C, (Found: C, 55.88; H, 5.75; N, 18.69. C₁₅H₁₉N₅. 1.1(C₂H₂O₄)
0.15H₂O requires C, 55.67; H, 5.84; N, 18.87%), δ (360MHz,
D₂O). 2.90 (6H, s, NMe₂), 3.22 (2H, t, J = 7.4Hz, CH₂), 3.46 (2H,
t, J = 7.4Hz, CH₂), 5.72 (2H, s, CH₂), 7.24 (1H, dd, J = 1.6 and
15 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H),
7.66 (1H, s, Ar-H), 7.79 (1H, s, Ar-H), 8.00 (1H, d, J = 1Hz, Ar-H)

EXAMPLE 11

20

3 - (2 - Aminoethyl) - 5 - (2 - methyl-tetrazol-5-yl)benzo[b]thiophene. Oxalate.

Step 1

25

4-Bromophenylmercaptopropanone

Step 3

5-Cyano-3-methyl benzo[b]thiophene

5 To copper (I) cyanide (0.569g, 6.35mmol) was added 5-bromo-3-methyl benzo[b]thiophene (1.179g, 5.19mmol) in N-methylpyrrolidinone (10ml) and the mixture was stirred at 180-190°C for 17h. This was then partitioned between ether (75ml) and ammonia solution (75ml). The ether layer was separated, washed with more ammonia solution (2 x 50ml), dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.81g of an off-white solid. Chromatography on flash silica, eluting with 10% ethyl acetate/petroleum ether yielded 0.76g (85%) of the title compound as a white solid. δ (CDCl_3) 2.47 (3H, s), 7.23 (1H, s), 7.55 (1H, dd, $J = 8.3$ and 1.5Hz), 7.93 (1H, d, $J = 8.4\text{Hz}$), 8.03 (1H, d, $J = 1.4\text{Hz}$).

Step 4

20 3-Methyl-5-(tetrazol-5-yl)-benzo[b]thiophene

25 To a solution of 5-cyano-3-methyl benzo[b]thiophene (0.194g, 1.12mmol) in N-methylpyrrolidinone (5ml) under nitrogen was added triethylamine hydrochloride (0.231g, 1.68mmol) followed by sodium azide (0.234g, 3.59mmol) and the mixture was extracted with ether (4 x 50ml). The combined ether extracts were dried (Mg SO_4) and evaporated *in vacuo* to

To a stirred solution of 4-bromothiophenol (5.09g, 26.9mmol) in NaOH (1.08g, 26.9mmol) and water (32ml) was added chloroacetone (2.17ml, 27.3mmol) and the mixture was stirred under nitrogen for 45min before extracting with ether, washing with water, drying (Na_2SO_4) and evaporating *in vacuo*, leaving 6.89g (100%) of the title compound as a white solid, δ (CDCl_3) 2.27 (3H, s), 3.65 (2H, s), 7.20 (2H, d, J = 8.5Hz), 7.41 (2H, d, J = 8.5Hz).

10

Step 2

5-Bromo-3-methyl benzo[b]thiophene

To a gently refluxing mixture of polyphosphoric acid (4.47g) and chlorobenzene (100ml) was added 4-bromophenylmercaptopropanone (2.24g, 9.14mmol) portionwise over 1h and the mixture was heated at reflux for 8 days. After cooling the organic phase was decanted off and the residue was decomposed with H_2O (~100ml), extracted with CH_2Cl_2 (2 x 75ml), dried (MgSO_4) and combined with the decanted organic phase. This was evaporated *in vacuo* to leave 2.096g of brown oil. Distillation on a Kugelröhren apparatus yielded 1.83g (88%) of the title compound as a pale yellow liquid, bp 100-110°C/0.35mbar. δ (CDCl_3) 2.41 (3H, s), 7.10 (1H, s), 7.43 (1H, dd, J = 8.5 and 1.9Hz), 7.69 (1H, d, J = 8.5Hz), 7.64 (1H, d, J = 1.9Hz).

leave 0.78g of a white solid. This was chromatographed on flash silica, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$ (aq) (40:8:1 to 30:8:1), to give 0.246g (100%) of the title product as a white solid. δ (DMSO) 2.46 (3H, s), 7.41 (1H, s), 7.98 (1H, d, $J = 8.4\text{Hz}$), 8.03 (1H, dd, $J = 8.4$ and 1.5Hz), 8.36 (1H, d, $J = 0.9\text{Hz}$). m/z (Cl^- , NH_3) 215 ($\text{M}-\text{H}$)⁻, 160.

Step 5

10 3-Methyl-5-(2-methyltetrazol-5-yl)benzo[b]thiophene and
 3-Methyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene

15 To a mixture of 3-Methyl-5-(tetrazol-5-yl) benzo[b]thiophene (0.241g, 1.12mmol) in acetonitrile (5ml) was added triethylamine (0.28ml, 2.01mmol), then iodomethane (0.486ml, 7.81mmol) followed by DMF (3ml) until a clear solution formed. The solution was stirred overnight under nitrogen before evaporating *in vacuo* and partitioning the residue between water (50ml) and ether (25ml). The aqueous layer was separated and extracted with more ether (2 x 25ml), the combined ether extracts were dried (Mg SO_4) and evaporated *in vacuo* to leave 0.241g of yellow solid. Chromatography on flash silica, eluting with 25-40% ethyl acetate/petroleum ether gave 0.168g (65%) of the 2-isomer of the title product as a white solid and 0.063g (24%) of the 1-isomer of the title product as a white solid. 2-isomer δ (CDCl_3) 2.52 (3H, s), 4.42 (3H, s), 7.14 (1H, s), 7.94 (1H, d, $J = 8.4\text{Hz}$), 8.10 (1H, dd,

J = 8.4 and 1.5Hz), 8.51 (1H, s). m/z (Cl⁺,NH₃) 231 (M+H)⁺ 1-isomer δ (CDCl₃) 2.50 (3H, s), 4.22 (3H, s), 4.22 (3H, s), 7.23 (1H, s), 7.64 (1H, dd, J = 8.3 and 1.5Hz), 8.03 (1H, d, J = 8.4Hz), 8.12 (1H, d, J = 1.6Hz). m/z (Cl⁺,NH₃) 231 (M+H)⁺, 202, 172.

5

Step 6

3-Cyanomethyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene

10 To a refluxing mixture of 3-methyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene (0.162g, 0.703mmol) and benzoyl peroxide (10.6mg) in carbon tetrachloride (10ml) irradiated with two desk lamps (2 x 60W) was added N-bromosuccinimide (0.126g, 0.707mmol) in small portions. After the addition was complete
15 the mixture was heated at reflux for a further 90 min, then filtered and the filtrate was evaporated *in vacuo* to leave an oil/solid mixture. Chromatography on flash silica, eluting with dichloromethane gave 0.161g of crude 3-bromomethyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene as a colourless oil.

20

The crude 3-bromomethyl-5-(2-methyl-tetrazol-5-yl) benzo[b]thiophene (0.145g) in DMSO (0.3ml) was added to a mixture of sodium cyanide (29.9mg, 0.61mmol) in DMSO (0.2ml)

and the mixture was stirred at 100°C for 2h. After cooling, the mixture was poured into water (10ml) and a brown solid was filtered off, washed with water and dried in a vacuum pistol to leave 73.5mg. The filtrate was extracted with dichloromethane (3 x 30ml) and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave 44.7mg. This was combined with the original solid and chromatographed on flash silica, eluting with 20-50% ethyl acetate/petroleum ether to yield 61.5mg (38%) of the title product as a white solid. δ (CDCl_3) 3.99 (2H, s), 4.43 (3H, s), 7.59 (1H, s), 8.00 (1H, d, J = 8.5Hz), 8.19 (1H, dd, J = 8.5 and 1.5Hz), 8.47 (1H, s).

Step 7

15 3-(2-Aminoethyl)-5-(2-methyl-tetrazol-5-yl)
benzo[b]thiophene. Oxalate.

20 To a solution of 3-cyanomethyl-5-(2-methyl-tetrazol-5-yl)
benzo[b]thiophene (0.434g, 1.70mmol) in THF (16ml) under
nitrogen was added dropwise 1.0M borane-tetrahydrofuran
complex in THF (5.10ml, 5.10mmol) and the mixture was heated
at reflux for 6h. After cooling in an ice-bath the mixture was
quenched with 2N HCl (22ml) and heated to reflux for 1h. The
THF was then removed *in vacuo* and the residue basified with
25 50% sodium hydroxide solution (4ml) before extracting with
dichloromethane (3 x 75ml). The combined extracts were dried
(K_2CO_3) and evaporated *in vacuo* to leave 0.45g.

Chromatography on flash silica eluting with CH₂Cl₂/MeOH/NH₃(aq) (60:8:1) gave 0.383g (87%) of the title product as a white solid. The oxalate salt was prepared using 5 exalic acid in methanol/ether to give the title product oxalate as a white solid, m.p. 204-209°C. Analysis found: C, 47.75; H, 4.28; N, 19.28%. Calcd for C₁₂H₁₃N₅S. 1.1 C₂H₂O₄: C, 47.59; H, 4.28; N, 19.54%. δ (DMSO) 3.17-3.21 (4H, m), 4.46 (3H, s), 7.72 (1H, s), 8.06 (1H, dd, J = 8.4 and 1.4Hz), 8.52(1H, s) m/z (CI⁺,NH₃) 260 (M+H)⁺, 230.

10

EXAMPLE 12

3-(2-Aminoethyl)-5-(1-methyltetrazol-5-yl)benzo[b]thiophene. Oxalate.

15

Step 1

3-Cyanomethyl-5-(1-methyltetrazol-5-yl)benzo[b]thiophene

20 Following the procedure of Example 11, Step 6, 0.666g (2.89 mmol) 3-methyl-5-(1-methyltetrazol-5-yl)benzo[b]thiophene was reacted with 0.515g (2.89mmol) of N-bromosuccinimide and 38.1mg of benzoyl peroxide in 30ml of carbon-tetrachloride. The reaction mixture was evaporated in 25 *vacuo* and chromatographed on flash silica, eluting with 0-3% methanol/dichloromethane to give 0.532g of crude 3-bromo-5-(1-

methyltetrazol-5-yl) benzo[b]thiophene.

The crude 3-bromo-5-(1-methyltetrazol-5-yl) benzo[b]thiophene (0.504g) was reacted with 97.7mg (1.99mmol) of sodium cyanide in 1.5ml of DMSO at 100°C for 2h. After cooling, the reaction mixture was poured into water (25ml) and extracted with dichloromethane (6 x 50ml). The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.37g. Chromatography on flash silica, eluting with 30-60% ethyl acetate/petroleum ether yielded 28.0mg (4%) of the title product. δ (CDCl_3) 4.00 (2H, s), 4.23 (3H, s), 7.63 (1H, s), 7.73 (1H, dd), 8.08 (1H, d), 8.15 (1H, d).

Step 2

15

3-(2-Aminoethyl)-5-(1-methyltetrazol-5-yl) benzo[b]thiophene. Oxalate.

Following the procedure of Example 11, Step 7, 26.1mg (0.102mmol) of 3-cyanomethyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene in 2ml of THF was reacted with 0.36ml (0.36mmol) of 1.0M borane-tetrahydrofuran complex in THF. Chromatography on flash silica, eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3(\text{aq})$ (60:8:1) gave 17.7mg (67%) of the title product as a colourless oil. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as a white solid, m.p. 206-212°C. Analysis found: C, 47.55; H, 4.05;

N, 19.65%. Calcd for $C_{12}H_{13}N_5S \cdot 1.1 C_2H_2O_4$: C, 47.59; H, 4.28; N, 19.54%. δ (D_2O) 3.32-3.35 (2H, m), 3.40-3.44 (2H, m), 4.22 (3H, s), 7.64 (1H, s), 7.73 (1H, d, $J = 8.4\text{Hz}$), 8.19 (1H, s), 8.22 (1H, d, 8.5Hz).

5

EXAMPLE 13

3-[2-(N,N-Dimethylamino)ethyl]-5-(2-methyltetrazol-5-yl)benzo[b]thiophene. Oxalate.

10

To a mixture of -(2-aminoethyl)-5-(2-methyltetrazol-5-yl)benzo[b]thiophene (0.372g, 1.43mmol) and sodium cyanoborohydride (0.136g, 3.15mmol) in methanol (3ml) and acetic acid (0.247ml, 4.30mmol) cooled in an ice bath was added 38% w/v formaldehyde solution (0.453ml, 5.74mmol) in methanol (3ml) dropwise over 5min and the mixture was stirred at room temperature for 3h. After this time, saturated potassium carbonate solution (30ml) was added and the mixture was extracted with ethyl acetate (3 x 50ml). The combined extracts were evaporated *in vacuo* to leave 0.53g. Chromatography on flash silica, eluting with 10-30% methanol/dichloromethane, gave 0.335g (81%) of the title product as a colourless oil. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as a white solid, m.p. 214-218°C. Analysis found: C, 50.58; H, 4.80; N, 18.28%. Calcd for $C_{14}H_{17}N_5S \cdot C_2H_2O_4$: C, 50.92; H, 5.07; N, 18.56%. δ (DMSO) 2.84 (6H, s), 3.30-3.42 (4H, m), 4.46 (3H, s), 7.69 (1H, s), 8.06 (1H, dd, $J = 8.4$ and 1.4Hz), 8.20 (1H, d, $J =$

15

20

25

8.4Hz), 8.56 (1H, s). m/z (Cl⁺,NH₃) 288 (M+H)⁺.

EXAMPLE 14

5 N,N-Dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Trisoxalate

1. 1-(4-Nitrophenyl)methyl-2-methylimidazole

10 Sodium hydride (2.45g; 61.0mmol, 60% dispersion in oil) was added to a solution of 2-methylimidazole (5.0g, 60.9mmol) in DMF (100ml). The mixture was stirred at room temperature for 0.25h before adding 4-nitrobenzyl bromide (13.2g, 61.0mmol) and heating at 110°C for 2h followed by stirring at room temperature for 16h. Water (200ml) and ethyl acetate (500ml) were added, the aqueous separated and extracted with ethyl acetate (2 x 500ml). The combined extracts were washed with water (3 x 250ml), dried (MgSO₄) and evaporated. The crude product was chromatographed on silica gel eluting with CH₂Cl₂/MeOH (4%) to give the title-product (1.58g, 10.5%); δ (360MHz, CDCl₃) 2.34 (3H, s, Me); 5.16 (2H, s, CH₂); 6.67 (1H, d, J = 1.3Hz, Ar-H); 7.03 (1H, d, J = 1.3Hz, Ar-H); 7.19 (2H, d, J = 9.5Hz, Ar-H); 8.22 (2H, d, J = 9.5Hz, Ar-H).

2. N,N-Dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Trisoxalate

Prepared from the preceding 4-nitrobenzyl imidazole using
5 the general procedure described for Example 5. The trisoxalate
salt was prepared, mp 160-163°C (MeOH/Et₂O); (Found: C,
50.57; H, 5.25; N, 10.60. C₁₇H₂₂N₄.2.8 (C₂H₂O₄) requires C,
50.79; H, 5.21; N, 10.48%); m/e 282 (M⁺); δ (360MHz, D₂O) 2.65
(3H, s, Me); 2.92 (6H, s, NMe₂); 3.25 (2H, t, J = 7.3Hz, CH₂);
10 3.50 (2H, t, J = 7.3Hz, CH₂); 5.42 (2H, s, CH₂); 7.18 (1H, d, J =
8.4Hz, Ar-H); 7.31-7.40 (2H, m, Ar-H); 7.40 (1H, s, Ar-H); 7.56
(1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

EXAMPLE 15

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N,N-Dimethyl-2-[5-imidazol-1-ylmethyl-1H-indol-3-yl]ethylamine Bisoxalate

Prepared from imidazole and 4-nitrobenzyl bromide using
20 the procedure described for Example 5. The bisoxalate salt was
prepared, 165-166°C (MeOH/Et₂O); (Found: C, 53.30; H, 5.34;
N, 12.18. C₁₆H₂₀N₄.2.05 (C₂H₂O₄) requires C, 53.30; H, 5.36;
N, 12.37%); δ (360MHz, D₂O) 2.92 (6H, s, NMe₂); 3.24 (2H, t, J
= 7.7Hz, CH₂); 3.48 (2H, t, J = 7.7Hz, CH₂); 5.50 (2H, s, CH₂);
25 7.27 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.37 (1H, s, Ar-H); 7.45
(1H, s, Ar-H); 7.49 (1H, s, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H);
7.75 (1H, s, Ar-H); 8.78 (1H, s, Ar-H).

EXAMPLE 16

5 N,N-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine Sesquioxalate

1. 1-(4-Nitrophenyl)-2-methylimidazole

Sodium hydride (4.87g, 122.0mmol, 60% dispersion in oil) 10 was added to a solution of 2-methylimidazole (10g, 122.0mmol) in DMF (100ml) and stirred at room temperature for 0.25h. 1-Fluoro-4-nitrobenzene (17.18g, 122.0mmol) was added to the reaction mixture and stirred at room temperature for 16h. Water (150ml) and ethyl acetate (250ml) were added; the aqueous separated and extracted with ethyl acetate (3 x 150ml). 15 The combined extracts were washed with water (3 x 150ml), dried (Na_2SO_4) and evaporated to give the desired product (11.5g, 47%); δ (360MHz, CDCl_3) 2.24 (3H, s, Me); 7.06 (1H, d, J = 1.5Hz, Ar-H); 7.10 (1H, d, J = 1.5Hz, Ar-H); 7.50 (2H, d, J = 20 9.5Hz, Ar-H); 8.38 (2H, d, J = 9.5Hz, Ar-H).

2. N,N-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine Sesquioxalate

25 Prepared from the preceding 4-nitrophenyl imidazole using the procedure described for Example 5. The sesquioxalate salt was prepared, mp 185-186°C (iPA/MeOH); (Found: C, 56.17; H, 5.99; N, 13.46. $\text{C}_{16}\text{H}_{20}\text{N}_4 \cdot 1.55(\text{C}_2\text{H}_2\text{O}_4)$. 0.1 EtOH requires C,

56.19; H, 5.79; N, 13.58%); δ (360MHz, D₂O) 2.55 (3H, s, Me);
2.93 (6H, s, NMe₂); 3.26 (2H, t, J = 7.4Hz, CH₂); 3.51 (2H, t, J =
7.4Hz, CH₂); 7.30 (1H, dd, J = 2.0 and 8.7Hz, Ar-H); 7.48 (1H, d,
J = 2.1Hz, Ar-H); 7.51-7.53 (2H, m, Ar-H); 7.70 (1H, d, J =
3.7Hz, Ar-H); 7.79 (1H, d, J = 2.0Hz, Ar-H).

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EXAMPLE 17

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N,N-Dimethyl-2-[5-(1,2,4-triazol-1ylmethyl)-1H-indol-3-yl]ethylamine. Succinate. Procedure B

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A solution of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride (2g, 7.6mmol, Example 5 step 3) and 4-N,N-dimethylaminobutanal dimethylacetal (1.8g, 11.2mmol) in 4% aqueous sulphuric acid (70ml) was heated at reflux for 2h. After the reaction mixture was cooled to room temperature, ethyl acetate (200ml) was added and the aqueous basified with K₂CO₃. The aqueous was separated and extracted further with ethyl acetate (2 x 150ml). The combined organics were dried (Na₂SO₄) and evaporated, and the residue chromatographed on silica gel eluting with CH₂Cl₂/EtOH/NH₃ (30:8:1) to give the title-triazole (610mg, 30%). The succinate salt was prepared by addition of a solution of succinic acid (0.27g, 2.3mmol) in methanol (3ml) to a solution of the triazole (0.61g, 2.3mmol) in methanol (5ml). The solvent was removed under vacuum and the resultant product recrystallised from isopropylalcohol, mp

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118-120°C; (Found: C, 58.76; H, 6.27; N, 17.79.

$C_{15}H_{19}N_3 \cdot C_4H_6O_4$ requires C, 58.90; H, 6.50; N, 18.08%).